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Breast Cancer Screening in the Era of Density Notification Legislation: Summary of 2014 Massachusetts Experience and Suggestion of An Evidence-Based Management Algorithm by Multi-disciplinary Expert Panel

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Abstract

Purpose—Stemming from breast density notification legislation in Massachusetts effective 2015, we sought to develop a collaborative evidence-based approach to density notification that could be used by practitioners across the state. Our goal was to develop an evidence-based consensus management algorithm to help patients and health care providers follow best practices to implement a coordinated, evidence-based, cost-effective, sustainable practice and to standardize care in recommendations for supplemental screening.

Methods—We formed the Massachusetts Breast Risk Education and Assessment Task Force (MA-BREAST) a multi-institutional, multi-disciplinary panel of expert radiologists, surgeons, primary care physicians, and oncologists to develop a collaborative approach to density notification legislation. Using evidence-based data from the Institute for Clinical and Economic Review (ICER), the Cochrane review, National Comprehensive Cancer Network (NCCN) guidelines, American Cancer Society (ACS) recommendations, and American College of

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Radiology (ACR) appropriateness criteria, the group collaboratively developed an evidence-based best-practices algorithm.

Results—The expert consensus algorithm uses breast density as one element in the risk stratification to determine the need for supplemental screening. Women with dense breasts and otherwise low risk (<15% lifetime risk), do not routinely require supplemental screening per the expert consensus. Women of high risk (>20% lifetime) should consider supplemental screening MRI in addition to routine mammography regardless of breast density.

Conclusion—We report the development of the multi-disciplinary collaborative approach to density notification. We propose a risk stratification algorithm to assess personal level of risk to determine the need for supplemental screening for an individual woman.

Background

Legislation regarding breast density notification is rapidly being implemented across the country. As of January 2015, 21/50 (42%) states have adopted legislation that requires patients undergoing screening mammography to be informed of their mammographic breast density as determined by the interpreting radiologist. In addition, federal legislation has been introduced, but is currently not active. State laws have been driven primarily by patient and grassroots advocacy organizations (e.g., http://www.areyoudenseadvocacy.org/) and differ in their implementation requirements. At a minimum, most laws require that the woman be informed that breast density may be a risk factor for breast cancer, may make cancer detection more difficult, and that additional supplemental screening may be indicated.

Further complicating the issue, most states have not mandated insurance coverage for supplemental screening tests [1]. This lack of coordinated coverage may increase health care disparities if the ability to self-pay for additional evaluation influences patient management.

There are currently no evidence-based recommendations for implementation of this legislation or to aid with patient and provider decision-making. Thus, the use of supplemental screening methods, particularly ultrasound, has varied among institutions, and even more widely among states. In the first year after adopting density notification legislation in Connecticut, some clinicians referred nearly all patients with dense breasts for supplemental screening ultrasound, while others referred none [2]. Further, only 45% of patients who received initial screening ultrasound actually returned for repeat screening ultrasound although they continued with annual mammography [2]. The lack of consensus, the subjective assessment of mammographic density, and the insufficient scientific evidence supporting widespread supplemental screening in women at average risk may be confusing to women and primary care providers.

The need for consensus and the formation of MA-BREAST

We formed the **M**assachusetts **B**reast **R**isk **E**ducation and **A**ssessment **T**ask Force (MA-BREAST) workgroup comprised of radiologists, breast surgeons, internal medicine specialists, and oncologists from academic and community based practices with the goals of [1] educating patients and physicians about the benefits, limitations, and risks of supplemental breast cancer screening and [2] developing a model of evidence-based

sustainable consensus recommendations for use of supplemental screening in dense breasts (Figure 1).

We used an evidence-based review of the literature, including the Institute for Clinical and Economic Review (ICER) report (together with the New England Comparative Effectiveness Public Advisory Council (CEPAC) and California Technology Assessment Forum (CTAF) reviews), the Cochrane review, the National Comprehensive Cancer Network (NCCN) guidelines, American Cancer Society (ACS) recommendations, the American College of Radiology appropriateness criteria, and the California Breast Density Information Group (CDBIG) algorithm [3–11]. We summarize the evidence and present our algorithm in this paper.

The risk of breast density and the goal of BI-RADS density classification

Mammographic breast density is an estimate of the amount of radio-opaque tissue (stromal and epithelial elements) relative to radio-lucent fatty tissue. Mammographic density does not correlate with physical exam [12–13]. When interpreting a mammogram, the radiologist classifies density using a subjective scale from the Breast Imaging Reporting and Data System (BI-RADS) as “almost entirely fat”, “scattered fibroglandular density”, “heteregeneously dense”, or “extremely dense” [14]. Although not in routine use, automated methods of density determination are also available. Dense breasts, defined as heterogeneously dense or extremely dense, are common, found in nearly 50% of the screening population. An estimated 1,250,585 women per year will require density notification in New England alone if legislation continues across the region [5]. This subjective assessment has limited intra- and inter-reader agreement, especially for the middle two density categories that may affect whether a woman is classified as “dense” or “not dense” [14–16]. Additionally, density is influenced by factors such as hormone status and weight changes [17]. Thus, a woman may be classified as having dense breasts one year, but not another (Figure 2).

Breast density primarily affects mammographic sensitivity by a masking phenomenon, where dense tissue may obscure an underlying malignancy [18–20]. Digital mammography has helped improve the sensitivity in dense breasts relative to fatty breasts [21, 22], however masking remains a challenge. Recent data suggests screening digital breast tomosynthesis may detect malignancies not seen on 2D mammography in women with dense breasts [23–24].

Dense breast tissue is also an independent risk factor for breast cancer with evidence suggesting that women with heterogeneously dense breasts have a 1.2-fold increased risk of breast cancer compared to the *average* patient’s risk, and women with extremely dense breasts have a 2.1-fold increased risk [25–26]. These more reasonable assessments differ from often quoted relative risks of 4–6x which are derived from comparing the densest breasts (10% of the population) with those with almost completely fatty breasts (10%) [18, 27–28].

Massachusetts Legislation Experience

In July 2014, breast density notification legislation was passed in Massachusetts [29]. When the Massachusetts Radiological Society became aware of potential legislation, introduced by lay activists, a coalition of academic and community radiologists engaged the state's legislative leadership. Initially, the coalition expressed reservations about the lack of insurance coverage and scientific evidence for widespread ultrasound screening and the subjective and unreliable nature of density measurement. However, as it became clear the legislation would pass, the coalition focused on ensuring the wording of the law would promote patient care and education, improved patient-physician communication, and cost-effective, evidence-based decision-making. Thus, the law encourages consultation between the patient and her referring provider to maximize education and decide about additional screening, but does not recommend or even mention specific supplemental screening modalities.

The group drafted a sample notification letter for patients that emphasizes that dense tissue is normal and common, and that density should be considered with other known breast cancer risk factors in determining overall risk status and deciding about supplemental screening (eTable 1). The use of a common educational letter for all patients undergoing mammography, with an individualized density statement, satisfies the legal notification requirements, and avoids falsely alarming women with dense breasts or falsely reassuring those without dense breasts who might otherwise be at high risk. The letter includes a link to an educational website (http://breast.massrad.org).

The coalition was unsuccessful in having the law mandate insurance coverage for the additional screening. Thus, additional screening may require self-pay, a potential burden for women with high-deductible insurance plans.

Screening modalities: benefits and limitations

Screening Mammography

Mammography, although imperfect, remains the only screening modality proven to demonstrate a decrease in breast cancer mortality [30]. Early detection by mammography yields a mortality reduction from breast cancer between 15–30% based on several large randomized controlled trials with 1–2 decades of follow-up [31–32]. Moreover, earlier cancer detection may limit the need for mastectomy, axillary dissection, and chemotherapy. At the low doses used today, the radiation risks are small to negligible in the screening age population. The mammographic cancer detection rate is 4–5 / 1000 in the average population. False positives are an important concern, with the mammographic recall rate (for additional imaging and/or biopsy) approximating 10% [3, 33]. For women who undergo 10 years of consecutive screening, approximately half will be called back for additional imaging at least once [34]. However, the positive predictive value for findings that undergo biopsy (PPV3) based on screening mammogram is moderately high, approximately 25–35% [3, 33]. For women with dense breasts, digital mammography has higher sensitivity than film-screen, approximating the sensitivity of fatty breasts, and is preferred. However, even in women with fatty breasts, mammography (digital or film-screen) misses approximately

12–22% of breast cancers [3,21, 35]. A negative mammogram may be reassuring but should not be considered proof that a woman does not have breast cancer.

Supplemental screening whole-breast ultrasound

No randomized controlled trials demonstrating mortality reduction in women who receive supplemental screening ultrasound exist. Data on supplemental screening ultrasound (US) in non-high risk women with dense breasts and negative mammography is limited. Using the ICER review and the American College of Radiology Imaging Network 6666 trial data, the best estimate of the incremental cancer detection rate (iCDR) in women at increased risk with a negative mammogram is approximately 2–3 / 1000 [3, 36]. But, the recall rate for additional imaging or follow-up imaging is at least 20% (twice that of mammography), and the positive predictive value of findings biopsied (PPV3) is approximately 6–8% (compared with 25–35% for mammography) [3]. Additionally, the biopsy rate is approximately triple that of mammography. Smaller studies suggest the iCDR of US in women with dense breasts and *average* risk is much lower, 1–2/1000 and PPV3 5–6% [2, 37]. This decrease in iCDR and PPV is to be expected given the decreased prevalence of disease in an average-risk group relative to women at high risk. Outcome models estimate that screening mammography may prevent 6 breast cancer deaths per 1000 women whereas supplemental ultrasound in women with negative mammography and dense breasts would prevent only an additional 0.36 deaths per 1000 [26].

Studies evaluating automated whole breast ultrasound are quite limited; however, initial reports suggest the cancer detection and predictive value is similar to standard hand-held ultrasound [3].

Supplemental screening MRI

Adjunctive screening MRI in women with negative mammograms has consistently been shown to be beneficial in women at high risk for breast cancer and is recommended by many leading societies including the ACS and NCCN for those with a known germline mutation in *BRCA1/2*, history of chest wall radiation before age 30, or a > 20–25% lifetime risk for breast cancer based on family history [8,9]. There is limited data on the use of supplemental MRI in women of low or average risk with dense breasts. However, using the numbers postulated from the ICER review, the iCDR in high-risk women is approximately 8 / 1000 and the positive predictive value for findings undergoing biopsy (PPV3) based on screening MRI is approximately 22–48% [3]. MRI is preferred over US for supplemental adjunctive screening in women of sufficiently high risk as it has a higher iCDR and a lower false positive rate than US [38]. Further, supplemental US does not improve the iCDR in women undergoing supplemental screening MRI [38].

Potential harms of Screening

The use of additional screening modalities among women with dense breasts would also incur harms, including cost, unnecessary recalls and biopsies, overdiagnosis / overtreatment, and possibly additional radiation. Screening ultrasound has a higher recall, biopsy, and false positive rate than mammography, which would create a significant public health burden if

used among the nearly 50% of women with mammographically dense breasts. Supplemental ultrasound is not cost-effective [26] and is not covered by many insurance companies, potentially exacerbating disparities in screening utilization and outcomes. Although studies have consistently shown that when MRI is limited to a high-risk population, the benefit of improved cancer detection outweighs the increased false positives, [3] MRI is expensive, prohibitive for patients with claustrophobia, and associated with the rare risks of contrast reactions and nephrogenic systemic fibrosis [39]. In addition, all screening modalities carry the risk of over-diagnosis, defined as the detection of a cancer by screening that would not have caused symptoms or death.

Evidence-Based Consensus Management Algorithm for Supplemental Screening

Risk Assessment

The Massachusetts legislation recommends a woman with mammographically determined dense breasts have a discussion with her primary care provider [29]. Similar to the California Breast Density Information Group (CDBIG) recommendations, MA-BREAST coalition supports a risk stratification approach for density notification that takes *all* of the patient's risk factors into account [11]. The risk assessment will determine if the patient should be referred for genetic counseling, considered for chemoprevention or prophylactic mastectomy, as well as inform the need for supplemental screening. Several prediction models exist to assess the probability of BRCA1/2 mutation or the probability of developing breast cancer, although all are imperfect and are particularly limited for non-white women [40] (Table 1). The ACS and the NCCN both suggest screening breast MRI for women with a greater than 20% lifetime risk of breast cancer based primarily on family history [8–9]. The ACS has approved the use of BRCAPRO, Tyrer-Cuzick and Claus models to determine eligibility for MRI, and specifically states not to use the Gail model for MRI determination, as it includes minimal family history [9]. NCCN guidelines for MRI are similar, and also include the BOADICEA model [8]. Although the Gail model is not recommended for determining the need for MRI, it is most widely accessible to patients and providers and may be an important first step in increasing the adoption of risk assessment in primary care if used to direct women to further counseling and in depth risk assessment. Currently, only a fraction of eligible women undergo screening MRI, suggesting that more widespread risk assessment is indicated [43].

Risk Stratified Supplemental Screening Algorithm

If a patient is eligible for genetic testing, she should be referred to a high-risk program or clinician for further risk stratification, for determination of the best screening and prevention approach.

For women NOT eligible for genetic testing (Figure 2), the following algorithm is supported by evidence and multiple national societies (Table 2):

If a patient is *low risk* (<15% lifetime), regardless of density—The patient should continue routine screening mammography. No supplemental screening is recommended

given the lack of evidence-based benefit of supplemental screening in low / average risk women balanced with the known high rate of false positives. However, in women with dense breasts, digital mammography is preferred over film/screen mammography. And early clinical data suggests that screening mammography with tomosynthesis may be preferred if available for women with dense breasts.

If a patient is *high risk* (>=20–25% lifetime by models based on family history), regardless of density—Adjunctive MRI should be added to routine mammography. If the patient is unable to receive MRI (gadolinium allergy, implantable device such as pacemaker, severe claustrophobia unresponsive to pre-medication, etc.), then supplemental screening ultrasound in addition to routine mammography is recommended.

If a patient is *intermediate risk* (>=15% and <20% lifetime)—The patient should discuss with her primary care provider the risks and benefits of supplemental screening. This risk group has insufficient evidence to recommend for or against supplemental screening. The ACR / Society of Breast Imaging appropriateness criteria state that MRI in intermediate risk women (demarcated as women with 15%–20% lifetime risk of breast cancer) is given a 7 out of 9 on the ACR guidelines appropriateness scale and may be appropriate for selected patients(10)

Screening US in this group is listed as 5 out of 9. NCCN guidelines recommend screening mammography without supplemental screening in this group. If the finding of dense breasts in the setting of other risk factors would increase a woman's lifetime risk of breast cancer to 15–20%, then supplemental screening could be considered after discussion regarding the risks of false positives and insurance issues.

Future

Our suggested algorithm is fluid because evidence continues to emerge regarding density, supplemental screening, risk stratification, and systems of care.

Additional promising screening modalities

Digital Breast Tomosynthesis (DBT)—Accumulating evidence demonstrates screening DBT reduces the recall rate relative to mammography while simultaneously increasing cancer detection [48]. Data suggest DBT minimizes the masking phenomenon from dense breasts [23–24]. The rapid clinical adoption of DBT may make DBT screening the standard in the future.

Dual-energy contrast-enhanced spectral mammography (CESM)—Using iodinated intravenous contrast, CESM could become a faster, cheaper and more widely available alternative to supplemental screening MRI. In the diagnostic setting, CESM has been shown to detect nearly all invasive cancers with fewer false positives than MRI [49].

Scintimammography (MIBI)—Scintimammography increases cancer detection when used as supplemental screening in dense breasts as the radiotracer uptake is independent

from mammographic density. Investigative techniques are emerging to reduce the radiation dose to a low level acceptable for widespread supplemental screening.

Fast MRI—An accelerated 3-minute screening protocol (as opposed to 20–45 minutes for a standard breast MRI) has been shown to be effective in women of mild to moderate risk of breast cancer. In an initial study of women with dense breasts and negative mammography and screening ultrasound, the negative predictive value of the Fast MRI was 99.8% and the incremental cancer detection rate was 18.3/1000 [50].

Risk Assessment Strategies

Multiple common and rare genomic variants have been identified that are associated with breast cancer risk. Although many of the currently known variants have yet to significantly improve breast cancer risk prediction, sequencing improvements will likely lead to a growing set of validated markers and the eventual inclusion of whole exome or even whole genome information in breast cancer risk prediction models. Furthermore, new methods for automated assessment of digital and 3D breast density and other imaging characteristics are being developed and may lead to substantial improvements in risk assessment in the near future.

Systems of Care

Health information technology offers an important opportunity to go beyond a “one size fits all” approach to density notification to more nuanced guidance and education about personal risk, risk reduction and screening. Perhaps most important, systems of care need to be held accountable for ensuring that women get the right test at the right time. Risk assessment algorithms need to be embedded into electronic health records, and updated with the availability of new evidence, so that decision support and reminders for providers are coordinated across the system.

Conclusion

We provide an evidence-based algorithm for risk stratification for breast cancer supplemental screening to address the concerns of patients, primary care providers, and radiologists that arise from breast density notification legislation. It is our hope that this may serve to educate patients and referrers, improve communication between a patient and her physician, and provide an outline to practice effective cost-efficient evidence-based medicine. In a letter from the authors of the BI-RADS, 5th edition, Drs. Carl D’Orsi and Ed Sickles state that: “the intent of BI-RADS density classification is simply to inform women with dense breasts that mammography is not as sensitive for depicting small breast cancers as it is for women with fatty breasts. It was not our intent to imply that all women with dense breasts, especially women with heterogeneously dense breasts, require supplementary screening with either ultrasound or MRI (personal communication 10/22/14 at 17:00).”

More attention needs to be directed toward systematic endeavors to ensure that women, primary care providers and radiologists are hearing and conveying consistent information. Legislation that has led to individual patient breast density notification may serve as an

opportunity to align the recommendations of primary providers, radiologists, and payors limiting confusion and possible liability. If the legislation creates better infrastructure for all stakeholders to collaborate, this could be a positive unanticipated benefit.

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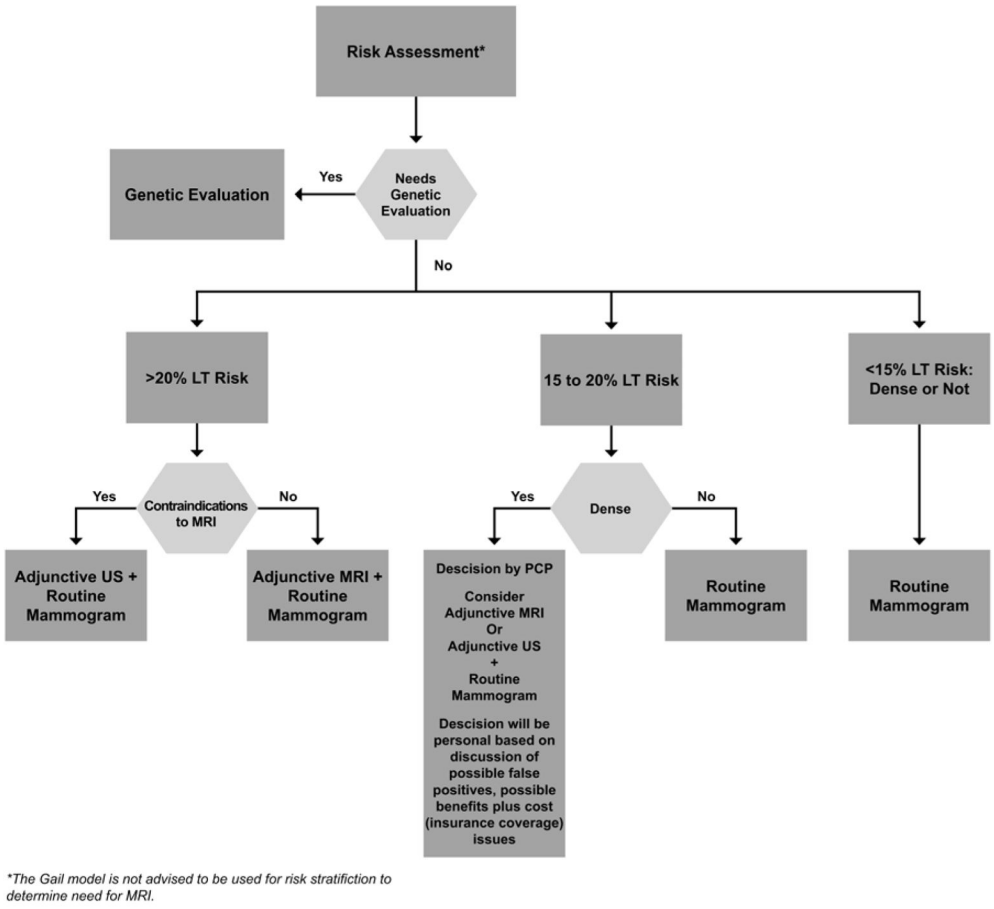

Figure 1.
Evidence-Based Suggested Algorithm for Use of Supplemental Screening

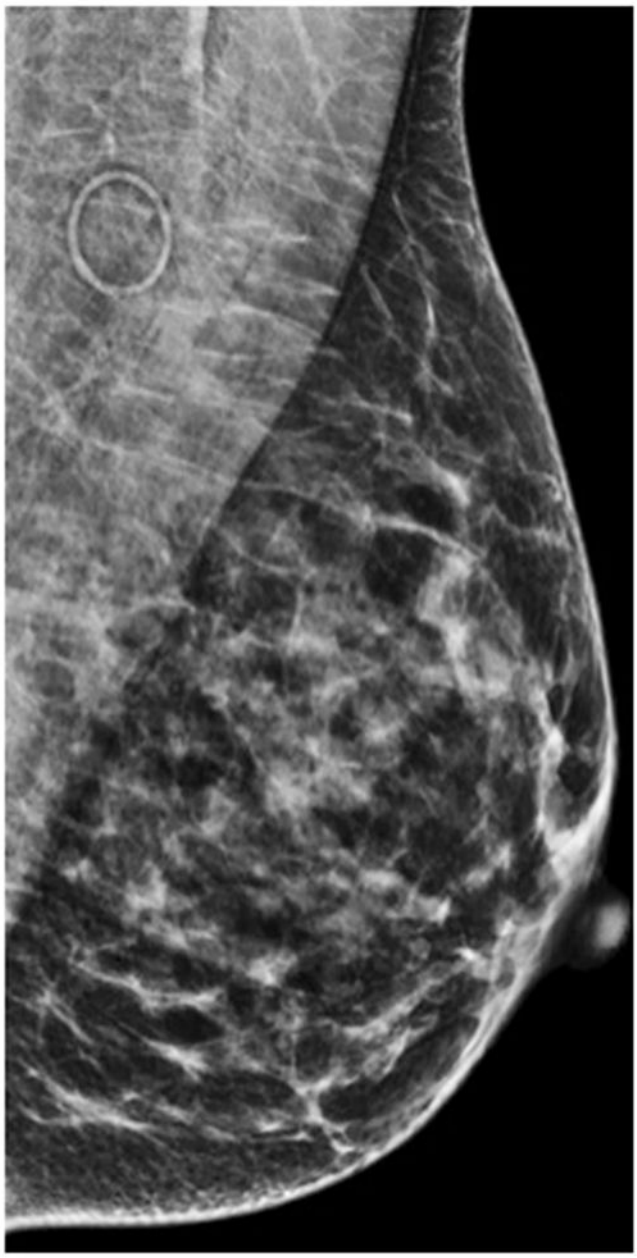

Figure 2.

Mammographic density inter-and intra-reader variability. A single medio-lateral oblique view normal mammogram in a 52 year old patient shows mammographic density that may be called heterogeneously dense (“dense”) by some radiologists and scatted fibroglandular tissue (“not dense”) by others, causing this patient and her provider to be confused if she receives density notification some years and not others.

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Table 1

Risk Models Summary (40–42)

Model Name	Accessible online	Guidelines Recommend MRI if >20–25%	Non-genetic risk factors included in model	Breast Density included in model	Comments	Major factors included in model
Gail	http://www.cancer.gov/bcrisktool/	No	Yes	No	Good to identify those needing chemoprevention	age at menarche, age at first birth, history of benign breast disease, limited family history of breast cancer.
Claus	http://young-ridge-2035.herokuapp.com/	ACS NCCN	No	No	Useful to determine need for MRI	Moderate family history
BRCAPRO	http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp http://66.118.159.147/HRAExpressEntry/(S(4tg4ye02imhoznxrjf25x0qe))/Default.aspx	ACS NCCN	No	No	Extremely good for determining hereditary risk, need for MRI, need for genetic testing	Extensive family history of breast and ovarian cancer including genetic testing results of patient and relatives.
BOADICEA*	http://ccge.medschl.cam.ac.uk/boadicea/	** NCCN	No	No	Extremely good for determining hereditary risk, need for MRI, need for	Extensive family history of breast and ovarian cancer including genetic testing results of patient and relatives.
Tyrer-Cuzick v6	http://66.118.159.147/HRAExpressEntry/(S(4tg4ye02imhoznxrjf25x0qe))/Default.aspx http://www.ems-trials.org/riskevaluator/	ACS NCCN	Yes	No	Extremely good for determining hereditary risk, need for MRI, need for genetic testing	age at menarche, age at menopause, age at first birth, history of benign breast disease, duration and intended duration of PMH use by type (estrogen, estrogen plus progesterone, or other) and timing (current *v* past), body-mass index (BMI), height, and moderate family history of breast cancer.
Tyrer-Cuzick v7	http://66.118.159.147/HRAExpressEntry/(S(4tg4ye02imhoznxrjf25x0qe))/Default.aspx http://www.ems-trials.org/riskevaluator/	ACS NCCN	Yes	No but likely in next version	Extremely good for determining hereditary risk, need for MRI, need for genetic testing	age at menarche, age at menopause, age at first birth, history of benign breast disease, duration and intended duration of PMH use by type

Model Name	Accessible online	Guidelines Recommend MRI if >20–25%	Non-genetic risk factors included in model	Breast Density included in model	Comments	Major factors included in model
						(estrogen, estrogen plus progesterone, (estrogen, estrogen plus progesterone, (estrogen, estrogenv plus progesterone, past), body-mass index (BMI), height, and moderate family history of breast and ovarian cancer.
Tice/BCSC Risk Calculator	https://tools.bcsc-scc.org/BC5yearRisk/	No	Yes	Yes	Good to identify those needing chemoprevention and possibly determining risk based screening	age at menarche, age at first birth, history of benign breast disease, limited family history of breast cancer, and density.
Rosner-Colditz	N/A	No	Yes	No	Good to identify those needing chemoprevention and possibly determining risk based screening	age at menarche, premenopausal duration (age at menopause minus age at menarche), postmenopausal duration (current age minus age at menopause), type of menopause, age at first birth minus age at menarche, birth index, history of benign breast disease, duration of PMH use by type (estrogen, estrogen plus progesterone, or other) and timing (current *v* past), body-mass index (BMI; trajectory from age 18 years to current), height, alcohol intake (from age 18 years to current), and limited family history of breast cancer.

Table 2

Major evidence based reviews, panels, or societal recommendations for screening modalities based on risk subgroups in women without known genetic mutations

Digital Mammography recommended (over Film) in women with dense breasts	**High Risk (>=20%) recommend Mammography + adjunctive MRI**	**Low Risk (<15%) and dense breasts NO supplemental screening routinely recommended**
National Comprehensive Cancer Network (NCCN) (8)	American Cancer Society (ACS) (9)	Cochrane Review (7)
CTAF* panel (4)	NCCN (8)	CTAF panel (4)
CEPAC** panel (5)	American College of Radiology (ACR) (10)	CEPAC panel (5)
	Society of Breast Imaging (SBI) (ACR) (10)	United States Preventive Task Force (USPSTF) (44)
	American Society of Breast Surgery (ASBS) (45)	NCCN (8)
	European Society of Breast Imaging (46)	American College of Obstetrics and Gynecology (ACOG) (47)
		ACR (10)
		SBI (ACR) (10)
		American Cancer Society (ACS) (9)

* CTAF = California Technology Assessment Forum

** CEPAC = New England Comparative Effectiveness Public Advisory Council